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Examiner's Amendment

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **Must** be submitted no later than the payment of the Issue Fee.

Examiner's Amendment Authorized

Authorization for this Examiner's Amendment was given in a fax transmission by Iver Cooper on April 28, 2004.

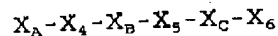
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-17 (cancelled).

18 (currently amended). A ~~non-naturally occurring polypeptide, or a~~ polypeptide in at least partially purified form, which is six to 20 amino acids in length, and which comprises the following sequence



wherein X_4 and X_5 are independently selected from the group consisting of Met, Ile, Leu, Val, norvaline, norleucine, methionine-S-oxide, N-methylvaline, N-methyl isoleucine, allo-leucine, and their D-isomers;

X_6 is selected from the group consisting of Asn, Asp, Gln, Glu, and their D-isomers,

X_A is L-Thr or D-Thr,

X_B is L-Lys, L-Orn, L-Dab, or one of their D-isomers, and

X_C is L-Arg or D-Arg,

wherein at least one of the following conditions (I)-(IV) ~~(V)~~ is true:

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I) at least one of X_A , X_B , X_C , X_4 , X_5 or X_6 is ~~an a non-~~
~~natural or unusual~~ amino acid other than a genetically encoded
amino acid, the genetically encoded amino acids being here
defined as amino acids selected from the group consisting of
glycine, L-alanine, L-serine, L-threonine, L-leucine, L-
isoleucine, L-methionine, L-valine, L-cysteine, L-asparagine,
L-aspartic acid, L-glutamine, L-glutamic acid, L-arginine, L-
lysine, L-histidine, L-phenylalanine, L-tryptophan, L-
tyrosine, and L-proline,

II) the polypeptide is cyclized,

~~III) the polypeptide is stabilized,~~

~~III) IV) the aminoterminal amino acid residue is~~
acylated, or

~~IV) V) the carboxyterminal amino acid residue is~~
amidated, said polypeptide having at least one of the
following properties:

a) induces inhibition of spontaneous IL-8 production by
human monocytes,

b) induces inhibition of IL-1 β induced IL-8 production
by human peripheral blood mononuclear cells (PBMC),

c) induces production of interleukin-1 receptor
antagonistic protein (IRAP) by human monocytes,

d) induces chemotactic migration of CD8+ human T
lymphocytes in vitro,

e) desensitizes human CD8+ T cells resulting in an
unresponsiveness towards rhIL-10,

f) suppresses the chemotactic response of CD4+ T human
lymphocytes towards IL-8,

g) suppresses the chemotactic response of human
monocytes towards MCAF/MCP-1,

h) inhibits class II MHC molecule expression on human
monocytes stimulated by IFN- γ ,

i) induces the production of IL-4 by cultured normal

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human CD4+ T cells,

j) reduces TNF α production in human mixed leukocyte reaction, or

k) downregulates TNF α and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

19 (currently amended). A polypeptide according to claim 18, which comprises the following sequence

X₃-Thr-X₄-Lys-X₅-Arg-X₆ (SEQ ID NO:20),

wherein

X₃, X₄ and X₅ are independently selected from the group consisting of Met, Ile, Leu and Val; and

X₆ is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of the following conditions (I)-(IV) ~~(V)~~ is true:

I) at least one of X₃, X₄, X₅, X₆, Thr, Lys, and Arg is independently substituted with ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid,

II) the polypeptide is cyclized,

~~III) the polypeptide is stabilized,~~

III) ~~IV)~~ the aminoterminal amino acid residue is acylated, or

IV) ~~V)~~ the carboxyterminal amino acid residue is amidated.

20 (currently amended). A polypeptide according to claim 18, which comprises the following sequence

X₂-X₃-Thr-X₄-Lys-X₅-Arg-X₆ (SEQ ID NO:21),

wherein

X₂ is Tyr or Phe,

X₃, X₄ and X₅ are independently selected from the group consisting of Met, Ile, Leu and Val; and

X₆ is selected from the group consisting of Asn, Asp, Gln and

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Glu,

wherein at least one of the following conditions (I) - ~~(IV)~~ ~~(V)~~ is true:

I) at least one of X_2 , X_3 , X_4 , X_5 , X_6 , Thr, Lys, and Arg is independently substituted with ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid,

II) the polypeptide is cyclized,

~~III) the polypeptide is stabilized,~~

~~III) IV)~~ the aminoterminal amino acid residue is acylated, or

~~IV) V)~~ the carboxyterminal amino acid residue is amidated.

21 (currently amended). A polypeptide according to claim 18, which comprises the following sequence

X_1 - X_2 - X_3 -Thr- X_4 -Lys- X_5 -Arg- X_6 (SEQ ID NO:22),

wherein

X_1 is Ala or Gly,

X_2 is Tyr or Phe,

X_3 , X_4 and X_5 are independently selected from the group consisting of Met, Ile, Leu and Val; and

X_6 is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of the following conditions (I) - ~~(IV)~~ ~~(V)~~ is true:

I) at least one of X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , Thr, Lys, and Arg is independently substituted with ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid,

II) the polypeptide is cyclized,

~~III) the polypeptide is stabilized,~~

~~III) IV)~~ the aminoterminal amino acid residue is acylated, or

~~IV) V)~~ the carboxyterminal amino acid residue is amidated.

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22 (currently amended). A polypeptide amounting to six to twenty amino acids which comprises the following sequence

Thr-X₄-Lys-X₅-Arg-X₆ (SEQ ID NO:19),

wherein

X₄ and X₅ are independently selected from the group consisting of Met, Ile, Leu and Val; and

X₆ is selected from the group consisting of Asn, Asp, Gln and Glu,

or which comprises a sequence which differs from SEQ ID NO:19 solely in that at least one of Thr, Lys, and Arg in SEQ ID NO:19 is independently substituted with ~~a non-natural or unusual~~ an amino acid selected from the group consisting of

Aad	2-Aminoadipic acid
bAad	3-Aminoadipic acid
bAla	beta-Alanine, beta-Aminopropionic acid
Abu	2-Aminobutyric acid
4Abu	4-Aminobutyric acid, piperidinic acid
Acp	6-Aminocaproic acid
Ahe	2-Aminoheptanoic acid
Aib	2-Aminoisobutyric acid
bAib	3-Aminoisobutyric acid
Apm	2-Aminopimelic acid
Dbu	2,4-Diaminobutyric acid
Des	Desmosine
Dpm	2,2'-Diaminopimelic acid
Dpr	2,3-Diaminopropionic acid
EtGly	N-Ethylglycine
EtAsn	N-Ethylasparagine
Hyl	Hydroxylysine
aHyl	alo-Hydroxylysine
3Hyp	3-Hydroxyproline
4Hyp	4-Hydroxyproline
Ide	Isodesmosine

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alle	allo-Isoleucine
MeGly	N-Methylglycine, sarcosine
MeIle	N-Methylisoleucine
MeLys	6-N-Methyllysine
MeVal	N-Methylvaline
Nva	Norvaline
Nle	Norleucine
and	
Orn	Ornithine,

said polypeptide having at least one of the properties defined in claim 18.

23-24 (cancelled).

25 (currently amended). A polypeptide according to claim 18 amounting consisting of up to 15 amino acids.

26 (currently amended). A polypeptide according to claim 18 amounting in total consisting of 10, 11, 12, 13, or 14 amino acids.

27 (currently amended). A polypeptide according to claim 18 amounting in total consisting of 9 amino acids.

28 (previously presented). The polypeptide of claim 21 wherein at least condition (I) is true.

29 (previously presented). The polypeptide of claim 20 wherein at least condition (I) is true.

30 (previously presented). The polypeptide of claim 19 wherein at least condition (I) is true.

31 (previously presented). The polypeptide of claim 18 wherein at least condition (I) is true.

32 (previously presented). The polypeptide of claim 18 which has the amino acid sequence Ala-Tyr-Met-Thr-Met-Lys-Ile-Arg-Asn (SEQ ID NO:1).

33 (cancelled).

34 (previously presented). A polypeptide according to claim 18 which is cyclized.

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35 (cancelled).

36 (previously presented). A polypeptide according to claim 18 wherein the aminoterminal amino acid residue is acylated.

37 (previously presented). A polypeptide according to claim 18 wherein the carboxyterminal amino acid residue is amidated.

38 (currently amended). A liposome comprising a polypeptide according to claim 18 ~~encapsulated in a liposome.~~

39 (previously presented). A polypeptide according to claim 18 in substantially pure form.

40 (cancelled).

41 (currently amended). A pharmaceutical composition comprising a polypeptide according to claim 18, or a salt, ester or solvate of said polypeptide, ~~or a peptidomimetic modelled on the basis of said polypeptide, where said peptidomimetic comprises an alpha-helical template.~~

42-50 (cancelled).

51 (currently amended). A method of treating ~~The method of claim 49 wherein the disease is acute pancreatitis which comprises administration of a therapeutically effective amount of the composition of claim 41.~~

52 (currently amended). A method of treating ~~The method of claim 49 in which the disease is ARDS-like syndrome which comprises administration of a therapeutically effective amount of the composition of claim 41.~~

53 (currently amended). ~~The method of claim 49 wherein acute pancreatitis is treated,~~ 51, further resulting in prevention of ARDS-like syndrome.

54-64 (cancelled).

65 (previously presented). The polypeptide of claim 18 where SEQ ID NO:19 is the C-terminal of said polypeptide and the polypeptide is not cyclized.

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66 (cancelled).

67 (previously presented). The polypeptide of claim 66 whose length does not exceed 10 amino acids.

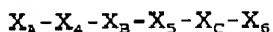
68 (currently amended). The polypeptide of claim 18, said polypeptide being selected from the group consisting of polypeptides identical to SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, and SEQ ID NO:22, except that at least one of conditions (I)-(IV) ~~(V)~~ applies.

69-73 (cancelled).

74 (previously presented). The polypeptide of claim 18 where said amino acids, other than X_A , X_B , X_C , X_4 , X_5 or X_6 , are alpha or beta amino acids.

75 (previously presented). The polypeptide of claim 18 which is not more than 15 a.a. in length.

76 (currently amended). A ~~non-naturally occurring polypeptide, or a~~ polypeptide in at least partially purified form, which is six to 20 amino acids in length, and which comprises the following sequence



X_A is L-Thr or ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid, the genetically encoded amino acids being here defined as amino acids selected from the group consisting of glycine, L-alanine, L-serine, L-threonine, L-leucine, L-isoleucine, L-methionine, L-valine, L-cysteine, L-asparagine, L-aspartic acid, L-glutamine, L-glutamic acid, L-arginine, L-lysine, L-histidine, L-phenylalanine, L-tryptophan, L-tyrosine, and L-proline,

X_B is L-Lys or ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid,

X_C is L-Arg or ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid,

X_4 and X_5 are independently selected from the group consisting of L-Met, L-Ile, L-Leu, L-Val and ~~a non-natural or unusual~~ an

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amino acid other than a genetically encoded amino acid,
X₆ is L-Asn, L-Asp, L-Gln, L-Glu, or ~~a non-naturally or unusual~~
an amino acid other than a genetically encoded amino acid,
no more than one of X_A, X_B, X_C, X₄, X₅ and X₆ is ~~a non-natural or~~
~~unusual~~ an amino acid which is other than a genetically
encoded amino acid and [[,]] other than the D-isomer of an L-
amino acid recited as possible at that position,
wherein at least one of the following conditions (I)-(IV) ~~(V)~~
is true:

I) at least one of X_A, X_B, X_C, X₄, X₅ or X₆ is ~~a non-natural~~
~~or unusual~~ an amino acid other than a genetically encoded
amino acid,

II) the polypeptide is cyclized,

~~III) the polypeptide is stabilized,~~

~~III) IV)~~ the aminoterminal amino acid residue is
acylated, or

~~IV) V)~~ the carboxyterminal amino acid residue is
amidated,

said polypeptide having at least one of the following
properties:

a) induces inhibition of spontaneous IL-8 production by
human monocytes,

b) induces inhibition of IL-1 β induced IL-8 production
by human peripheral blood mononuclear cells (PBMC),

c) induces production of interleukin-1 receptor
antagonistic protein (IRAP) by human monocytes,

d) induces chemotactic migration of CD8+ human T
lymphocytes in vitro,

e) desensitizes human CD8+ T cells resulting in an
unresponsiveness towards rhIL-10,

f) suppresses the chemotactic response of CD4+ T human
lymphocytes towards IL-8,

g) suppresses the chemotactic response of human

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monocytes towards MCAF/MCP-1,

h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- γ ,

i) induces the production of IL-4 by cultured normal human CD4+ T cells,

j) reduces TNF α production in human mixed leukocyte reaction, or

k) downregulates TNF α and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits, and wherein any non-natural or unusual amino acid referred to above is an amino acid selected from the group consisting of

Aad	2-Aminoadipic acid
bAad	3-Aminoadipic acid
bAla	beta-Alanine, beta-Aminopropionic acid
Abu	2-Aminobutyric acid
4Abu	4-Aminobutyric acid, piperidinic acid
Acp	6-Aminocaproic acid
Ahe	2-Aminoheptanoic acid
Aib	2-Aminoisobutyric acid
bAib	3-Aminoisobutyric acid
Apm	2-Aminopimelic acid
Dbu	2,4-Diaminobutyric acid
Des	Desmosine
Dpm	2,2'-Diaminopimelic acid
Dpr	2,3-Diaminopropionic acid
EtGly	N-Ethylglycine
EtAsn	N-Ethylasparagine
Hyl	Hydroxylysine
aHyl	alo-Hydroxylysine
3Hyp	3-Hydroxyproline
4Hyp	4-Hydroxyproline
Ide	Isodesmosine

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allo	allo-Isoleucine
MeGly	N-Methylglycine, sarcosine
MeIle	N-Methylisoleucine
MeLys	6-N-Methyllysine
MeVal	N-Methylvaline
Nva	Norvaline
Nle	Norleucine
and	
Orn	Ornithine.

77 (currently amended). The polypeptide of claim 76 where no more than one of the amino acids of said polypeptide which lie outside said sequence, if any, is ~~a non-natural or unusual~~ an amino acid other than a genetically encoded amino acid and other than a D-isomer of one of the genetically encoded amino acids.

78 (previously presented). The polypeptide of claim 76 which is not more than 15 a.a. in length.

79 (previously presented). The polypeptide of claim 77 which is not more than 15 a.a. in length.

80-81 (cancelled).

82 (previously presented). The polypeptide of claim 18 where

X₁ and/or X₂ are independently selected from the group consisting of Met, Ile, Leu, Val, norvaline, norleucine, N-methylvaline, N-methyl isoleucine, allo-leucine, and their D-isomers, and

X₃ is L-Lys, L-Orn, or one of their D-isomers.

83-87 (cancelled).

88 (previously presented). The polypeptide of claim 18 where SEQ ID NO:19 is the C-terminal of said polypeptide.

89-91 (cancelled).